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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/898,887 | 07/03/2001 | Raghavan Rajagopalan | MRD-61 | 2188 |

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| EXAMINER | |
|---|---|
| LUKTON, DAVID | |
| ART UNIT | PAPER NUMBER |
| 1653 | |

DATE MAILED: 03/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/898,887 | RAJAGOPALAN ET AL. | |
| | Examiner | Art Unit | |
| | David Lukton | 1653 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *03 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *15-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Pursuant to preliminary amendment, claims 1-14 have been cancelled, and claims 37-46 added. Claims 15-46 are pending.

Applicants' species elections are acknowledged.

✧

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method of performing a "phototherapeutic procedure". The term "therapy" (or phototherapy) implies an assertion that an ill patient can be treated such that manifestations of the illness are ameliorated. However, there is no evidence that this will happen in the instant case. If one takes a "drug" that has been shown to be effective in one way or another, and subsequently endeavors to create a "prodrug" thereof, "unpredictable" effects *in vivo* can result. Consider the following:

- Shabat D. (*Proceedings of the National Academy of Sciences* **98** (13) 7528-33, 2001)

discloses a prodrug that is not activated by endogenous enzymes. This supports the conclusion of "unpredictability" in that the instantly claimed compounds may not be activated by endogenous enzymes.

- Smal (*Biochemical Pharmacology* **49** (4) 567-74, 1995) discloses (e.g., p. 572) that 2-Leu-MTX is unsuitable as a prodrug

- Saboulard (*Molecular Pharmacology* **56** (4) 693-704, 1999) discloses (e.g., page 701, col 1) that prodrugs of AZT are not effective.

- Jaffar (*Bioorganic and Medicinal Chemistry Letters* **9** (1) 113-8, 1999) discloses (e.g., table 1) prodrugs of aspirin that are not effective.

- Deverre J. R. (*Pharmaceutica Acta Helvetiae* **67** (12) 349-52, 1992) prepared a prodrug, and discovered inactivity of the prodrug *in vivo*, either by the oral route (10 mM) or after an intraperitoneal administration (1 mM).

- Miyauchi M (*Chemical and Pharmaceutical Bulletin* **38** (7) 1906-10, 1990) discloses an attempt to produce orally bioavailable prodrugs of 3-thiazoliomethyl cephalosporin (compound number 1) Lipophilicity of the resulting derivatives (8-10) was suitable for passive absorption from the intestinal tract, and chemical stability in phosphate buffer solution (pH 6.86) was moderate. However, when administered orally to mice, these derivatives were mainly transformed to a novel 3-spiro cephalosporin 11, and desired reconversion to the 3-thiazoliomethyl cephalosporin was minor. These results showed that the derivatives (8-10) tested in this study did not serve as orally active prodrugs of 3-thiazoliomethyl cephalosporin 1.

- Hadad S (*Journal of Pharmaceutical Sciences*, **81** (10) 1047-50, 1992) examined the pharmacokinetics and efficacy of five monoester prodrugs of valproic acid (VPA). Valproic acid an anti-epileptic drug. Four of the five prodrugs were ineffective in mitigating symptoms of epilepsy. In addition, a pharmacokinetic- pharmacodynamic correlation was absent in the case of B-VPA and H-VPA.

- Langer (*J. Med. Chem.* **44**, 1341-1348, 2001) has examined the effects of bonding a peptide, via a linker, to daunorubicin and doxorubicin. As stated (p. 1344, col 1, paragraph 3, attaching a peptide to the amino group of daunorubicin or doxorubicin eliminated activity.

- Mamber S. W. (*Journal of Pharmacology and Experimental Therapeutics* **274** (2) 877-883, 1995) discloses prodrugs of taxol. The 2'- and 7- phosphate analogs BMY46366 and BMY46489 were ineffective as prodrugs.

- Niemi (*J. Med. Chem.* **42**, 5053, 1999) prepared compounds which were intended to be prodrugs of clodronic acid. As it happened, benzoyloxyproyl esters of clodronic acid were ineffective as prodrugs.

None of the foregoing references pertain to photodynamic therapy specifically. However, consider the following:

- Hillemanns, P. (*International journal of cancer. Journal international du cancer*, 81 (1) 34-8, 1999) discloses that photodynamic therapy is not effective to treat cervical intraepithelial neoplasia

- Li W. (*Journal of photochemistry and photobiology. B, Biology* 60 (2-3) 79-86, 2001) discloses that photodynamic therapy is not effective when applied to K562 cells.

- Anderson Gregory S (*Journal of photochemistry and photobiology. B, Biology* 68, (2-3) 101-8, 2002) discloses that solid tumor cells are refractory to photodynamic therapy.

- Grossweiner L. I. (*Photochemistry and photobiology* **46** (5) 911-7, 1987) discloses (table 4, page 916) that photodynamic therapy was not effective when administered to a male patient with a tumor located in the anterior tonsillar pillar.

- Pope A.J. (*Journal of urology* 145 (5) 1064-70, 1991) discloses (e.g., page 1068, col 2) that photodynamic therapy is not effective with subjects afflicted with invasive tumors.

- Gluckman J. L. (*Laryngoscope* 101 (1 Pt 1) 36-42, 1991) discloses that photodynamic therapy was not effective in several patients with advanced head and neck cancer.

Clearly, if one takes a compound which has been shown to be therapeutically effective, and attaches a group or substitutent to it, the result is often loss of activity. Thus, one cannot "predict" therapeutic efficacy of a prodrug on the basis of efficacy of the "parent" drug. This is true whether the patient is being exposed to light or not. In addition, as is evident from the references, attempts to perform a phototherapeutic procedure lead to "unpredictable" results.

Accordingly, in view of the unpredictability of the art, the absence of any working examples, the absence of any guidance as to which compounds will be effective, and the state of the art, it is fair to conclude that "undue experimentation" would be required to perform a phototherapeutic procedure on an ill patient, given that the term "therapeutic" means that symptoms of the disease will be ameliorated.

A matter separate from the foregoing, is that applicants have not shown that the compounds (to which the claims are directed) are effective as photosensitizers, even *in vitro*. One cannot predict the propensity of a compound to act as a photosensitizer merely by viewing its structure. This issue is of significance because, *to the extent* that photodynamic therapy has proven effective in the past, efficacy has been dependent on the ability of the compounds to act as photosensitizers. In the presence of light, photosensitizers facilitate the transfer of energy to oxygen, resulting in the production of singlet oxygen. The presence of singlet oxygen leads to a variety of effects *in vivo*, including damage to cell membranes,

vascular injury and coagulation. "Downstream" from this is neutrophil activation, platelet activation, and production of prostaglandins and thromboxane. However, applicants have not shown that the disclosed compounds function as photosensitizers, or that they can facilitate the production of singlet oxygen.

❊

Claims 15-46 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are drawn to a method of performing a "phototherapeutic procedure". The claims are indefinite as to what the objectives might be, and what the manifestations of a successfully completed procedure might be.

In claim 15 (third line from last), the term "tissues" (in the plural) lacks antecedent basis, notwithstanding the prior recitation of the term "tissue" (in the singular).

✧

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at 571-272-0951. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

D. Lukton

DAVID LUKTON
PATENT EXAMINER
GROUP 1600